REMARKS

Reconsideration of the rejections set forth in the Office action mailed March 21, 2006 is respectfully requested. Claims 1-10 are pending in the application. Claims 1-6 are currently withdrawn from consideration, and claims 7-10 are under examination.

I. Amendments

Claim 7 has been amended for clarity. For example, the steps have been given the letters (a) – (g) to indicate the order of steps carried out, as described at pages 20-21 and illustrated in Figure 12 of the specification.

Support for the amendment to the preamble is found, for example, at page 3, lines 22-23 of the specification.

Support for the description of the Exo III resistant linker as "comprising a 3'-overhang" is found at page 20, lines 6-8 of the specification. Support for the description of the Exo III susceptible linker as "comprising either a 5'-overhang or a blunt end" is found at page 20, lines 15-16 of the specification.

The claim specifies that the second endonuclease has a cleavage site different from that of said first restriction endonuclease, which is apparent from the illustration of an embodiment of the process shown in Figure 12, particularly in step (3).

The claim has been amended for clarity to state that "those fragments produced by cleavage with said second restriction endonuclease", rather than "some" of the fragments, comprise a second cleavage end. This is also apparent from step (3) of the embodiment of Figure 12.

Support for the phrase "to isolate duplexes containing said Exo III susceptible linker" in step (g) is found, for example, at the paragraph bridging pages 20-21 of the specification.

The specification has been amended to add reference numbers present in the drawings.

A replacement drawing sheet is provided for Figure 2B. The reference numbers (126) and (236) have been deleted.

No new matter is added by any of the amendments.

II. Information Disclosure Statement

The Examiner stated that a non-patent cited reference was missing from the Information Disclosure Statement sent March 11, 2003. A copy of this reference will be sent shortly in a Supplemental IDS.

III. Drawings

The specification has been amended, as requested, to add reference numbers present in the drawings, with the following exception: The reference numbers (126) and (236) have been deleted from Figure 2B. A replacement drawing sheet is provided for Figure 2B.

IV. Rejections under 35 U.S.C. §112, First Paragraph

Claims 7-10 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

This rejection is respectfully traversed in view of the following remarks.

The MPEP, in the section entitled "Methodology for Determining Adequacy of Written Description", directs Examiners to: (1) "For Each Claim, Determine What the Claim as a Whole Covers"; (2) "Review the Entire Application to Understand How Applicant Provides Support for the Claimed Invention Including Each Element and/or Step"; and (3) "Determine Whether There is Sufficient Written Description to Inform a Skilled Artisan That Applicant was in Possession of the Claimed Invention as a Whole at the Time the Application Was Filed" (emphasis added).

The applicant feels that the current rejection is misdirected, since the Examiner's remarks appear to treat the claims as claims to a reference library; that is, to a product, rather than to a method. For example, in item 10 on page 6 of the Office Action, the Examiner refers to "the claimed 'reference library", followed by case law which discusses what is needed to "adequately describe a product". However, the claims are not directed to a reference library, or to any other product. The Office Action includes many other citations of

case law which are concerned with claims to nucleic acid materials; again, these citations are not pertinent to the present claims, which do not claim any materials or products.

The Examiner does appear to approach this issue by citing the following case law:

"Regardless of whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods" (page 6 of Office Action).

However, the cited case (*University of Rochester v. G.D. Searle & Co., Inc. et al.*, CAFC 2004) goes further to state that the "claimed method depends on finding a compound that selectively inhibits PGHS-2 activity. Without such a compound, it is impossible to practice the claimed method of treatment." This scenario, where the nature of the disclosed compound is critical to the claimed method, is quite different from the currently claimed method, which can be carried out on essentially any DNA sample, using the described enzymes and linkers, whose selection would be within the ability of one skilled in the art. (The absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 U.S.C. 112, para. 1, for lack of adequate written description (MPEP § 2163 II.A.1); What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94 (MPEP § 2163 II.A.3(a).)

To present an analogy, requiring a description of every nucleic acid that could be used in the presently claimed method would be analogous to requiring an inventor who claimed, for example, a new method of reducing a ketone, to describe every possible ketone that could be reduced using his method.

Referring again to the case law cited by the Examiner on page 6, the inventor's description must be "sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". In the present case, a practitioner is clearly apprised of the metes and bounds of the claim, in view of the clear description of steps (a)-(g) of the claimed method. A practitioner who carries out steps (a)-(g) of claim 7 on any "pooled nucleic acid", using a "first restriction endonuclease", an "Exo

III resistant linker, comprising a 3'-overhang", a "second restriction endonuclease, having a cleavage site different from that of said first restriction endonuclease", an "Exo III susceptible linker, comprising either a 5'-overhang or a blunt end", "a first member of a binding pair", Exo III, and "a second member of said binding pair", would be infringing the claim.

In view of the foregoing, the applicant submits that claims 7-10 comply with the requirements of 35 U.S.C. §112, first paragraph.

V. Rejections under 35 U.S.C. §112, Second Paragraph

Claims 7-10 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms objected to include the use of "second cleavage end" and "second cleavage ends" (item 15 of Office Action). The second term has been amended to "each said second cleavage end" to remove the perceived discrepancy.

In response to item 16 of the Office Action, the term "first restriction sites" has been deleted from the claim (which does not include the term "second restriction sites"). In addition, the claim now specifies that the "second restriction endonuclease" has "a cleavage site different from that of said first restriction endonuclease". The steps in the claim have been given the letters (a) – (g) to indicate the order of steps carried out, as described at pages 20-21 and illustrated in Figure 12 of the specification.

In response to item 17 of the Office Action, the claim has been amended to state that "those fragments produced by cleavage with said second restriction endonuclease", rather than "some" of the fragments, comprise a second cleavage end. This fact is apparent from the illustration of step (3) of the embodiment of Figure 12.

In response to item 18 of the Office Action, the Exo III resistant linker is described as "comprising a 3'-overhang", and the Exo III susceptible linker is described as "comprising either a 5'-overhang or a blunt end", as noted at page 20 of the specification.

In view of the foregoing, the applicant submits that claims 7-10 comply with the requirements of 35 U.S.C. §112, second paragraph.

VI. Rejections under 35 U.S.C. §102(e)

Independent claim 7 was rejected under 35 U.S.C. §102(b) as being anticipated by Short *et al.*, U.S. Patent No. 6,352,842. This rejection is respectfully traversed for the following reasons.

A. The Claim

Independent claim 7 is directed to a method of making a reference library comprising a mixture of heterogeneous nucleic acid fragments which has been enriched for polymorphic sequences, the method comprising:

(a) digesting pooled nucleic acid with a first restriction endonuclease, to produce a first mixture of restriction fragments having first cleavage ends;

(b) ligating an Exo III resistant linker, comprising a 3'-overhang, to the first cleavage ends of said restriction fragments, to form a first ligation product population;

(c) digesting said first ligation product population with a second restriction endonuclease, having a cleavage site different from that of said first restriction endonuclease, to form a second mixture of restriction fragments, wherein those fragments produced by cleavage with said second restriction endonuclease comprise a second cleavage end;

(d) ligating an Exo III susceptible linker, comprising either a 5'-overhang or a blunt end, to each said second cleavage end, to form a second ligation product population,

wherein said Exo III susceptible linker comprises a first member of a binding pair;

(e) digesting said second ligation product population with Exo III to form a third ligation product population, comprising (i) single stranded DNA comprising end sequences corresponding to said Exo III resistant and Exo III susceptible linkers and (ii) double stranded DNA comprising end sequences corresponding to said Exo III resistant linkers;

(f) denaturing said third ligation product population and hybridizing the mixture so obtained to form a reannealed third ligation product population; and

(g) contacting said reannealed third ligation product population with a second member of said binding pair to isolate duplexes containing said Exo III susceptible linker, thereby to enrich for duplexes which form a polymorphic reference population of restriction fragments.

B. The Cited Art

The Short *et al.* patent teaches a "directed evolution method for preparing a polynucleotides encoding polypeptide [sic], which method comprises the step of generating site-directed mutagenesis optionally in combination with the step of polynucleotide chimerization, the step of selecting for potentially desirable progeny molecules, including by a process termed end-selection (which may then be screened further), and the step of screening the polynucleotides for the production of polypeptide(s) having a useful property" (Field of the Invention).

The Examiner points to different locations in the specification of Short *et al.* that describe steps such as: digesting nucleic acids with restriction enzymes; producing Exo III resistant or susceptible linkers; ligation; denaturing and hybridization of nucleic acids; and binding and enriching of nucleic acids. The locations cited by the Examiner typically include general definitions of these processes and/or their use in the methods described in Short *et al.*, which bear no relation to the method embodied by steps (a) – (g) of the applicant's claim.

For a prior art reference to anticipate in terms of 35 U.S.C. §102, every element of the claimed invention must be identically shown in a single reference. ...The elements must be arranged as in the claim under review... *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). (MPEP §2131)

The Short *et al.* patent in no way teaches the method embodied by steps (a) – (g) of the applicant's claim. Accordingly, the applicant respectfully requests that this rejection the rejection under 35 U.S.C. §102(e) be withdrawn.

VII. Further Rejections under 35 U.S.C. §102(e)

Independent claim 7 and dependent claims 8-9 were rejected under 35 U.S.C. §102(e) as being anticipated by Barany *et al.*, U.S. Patent No. 6,027,889. This rejection is respectfully traversed for the following reasons.

A. The Claims

Independent claim 7 is described above; dependent claims 8-9 include all of the limitations of claim 7.

B. The Cited Art

Barany *et al.* is directed to "the detection of nucleic acid sequence differences using coupled ligase detection reaction and polymerase chain reaction" (Abstract; Summary). The Examiner states that Barany *et al.* teach various PCR and LDR methods "to form a library of nucleic acids"; however, the term "library" does not appear at the cited location, nor anywhere else in the reference.

Similar to the treatment of Short *et al.*, above, the Examiner points to different locations in the specification of Barany *et al.* that describe steps such as: digesting genomic DNA with restriction enzymes; employing Exo III resistant or susceptible linkers; denaturing and hybridization of nucleic acids; and contacting nucleic acids to a solid support (which in Barany *et al.* refers to an array of probe sequences). The locations cited by the Examiner describe the use of these processes in the methods described in Barany *et al.*, which bear no relation to the method embodied in steps (a) – (g) of the applicant's claim.

For a prior art reference to anticipate in terms of 35 U.S.C. §102, every element of the claimed invention must be identically shown in a single reference. ...The elements must be arranged as in the claim under review... *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). (MPEP §2131)

The Barany *et al.* patent in no way teaches the method embodied by steps (a) – (g) of the applicant's claim. Accordingly, the applicant respectfully requests that this rejection under 35 U.S.C. §102(e) be withdrawn.

VIII. Rejections under 35 U.S.C. §103(a)

Claims 7-10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Short *et al.*, cited above, and Strathmann, U.S. Patent No. 6,480,791. The rejections are respectfully traversed in light of the following remarks.

A. The Claims

Independent claim 7 is described above; dependent claims 8-10 contain all the limitations of claim 7.

B. The Cited Art

As stated above, the disclosure of Short *et al.* describes various processes used in

manipulations of nucleic acids, including restriction enzyme digestion, ligation of linkers, hybridization, etc., but it in no way teaches the method embodied in steps (a) – (g) of the applicant's claim.

As stated by the Examiner, Strathmann likewise teaches methods of nucleic acid amplification and sequencing, as well as the use of S1 and mung bean nuclease, the single-strand dependent nuclease Exo I, and biotin.

However, the two references, taken alone or in combination, clearly do not teach or suggest the method embodied by steps (a) – (g) of the applicant's independent claim. The teachings of Strathmann do not make up for the deficiencies of Short *et al.*, described above, in this regard.

In view of the foregoing, the applicant respectfully requests the Examiner to withdraw the rejection under 35 U.S.C. §103(a).

IX. Further Rejections under 35 U.S.C. §103(a)

Claims 7-10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Barany *et al.*, U.S. Patent No. 6,027,889, cited above, and Barany *et al.*, U.S. Patent No. 6,534,293. The rejections are respectfully traversed in light of the following remarks.

A. The Claims

Independent claim 7 is described above; dependent claims 8-10 contain all the limitations of claim 7.

B. The Cited Art

As stated above, the disclosure of Barany *et al.* ('889) describes various processes used in manipulations of nucleic acids, including restriction enzyme digestion, ligation of linkers, hybridization, etc., but it in no way teaches the method embodied in steps (a) – (g) of the applicant's independent claim.

Barany et al. ('293) is directed to methods of "assembling genomic maps of an organism's DNA or portions thereof" (Summary of the Invention). This reference does not teach or suggest the method embodied in steps (a) – (g) of the applicant's independent claim.

The Examiner states that it would have been obvious to modify the process of Barany *et al.* ('889) using the biotin tag of Barany et al. ('293). However, such a modification clearly

would not produce the process claimed by the applicants, since the two references, taken alone in combination, in no way teach or suggest this process.

In view of the foregoing, the applicant respectfully requests the Examiner to withdraw the rejection under 35 U.S.C. §103(a).

X. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

Respectfully submitted,

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